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PTO FORM 1449 - Supplemental

ATTY. DOCKET NO.

03678.0073.DVUS04

APPLICATION NO.

10/682,545

APPLICANT

Ward M. Peterson et al.

FILING DATE

October 8, 2003

GROUP

1623

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	1.						
	2.						
	3.						

FOREIGN PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
<i>dm</i>	4.	WO 98/34593	13.08.98	PCT	A61K	9/00	Y	
	5.							
	6.							

OTHER REFERENCES

(Including Author, Title, Date, Pertinent Pages, Etc.)

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*dehane**10/15/05*

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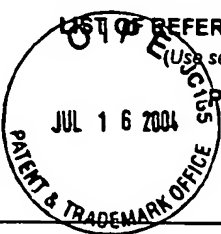
U.S. PATENT DOCUMENTS							
*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
<i>mu</i>	1.	US 6,319,908 B1	11/20/01	Yerxa et al.	514	51	07/24/98
	2.	US 6,548,658 B2	04/15/03	Yerxa	536	26.22	11/20/01
	3.	US 6,555,675 B2	04/29/03	Rideout et al.	536	25.6	03/23/01
	4.	US 6,596,725 B2	07/22/03	Peterson et al.	514	256	01/30/01
	5.	US 6,673,779 B2	01/06/04	Jacobus et al.	514	51	06/05/02
<i>mu</i>	6.	US 6,696,425 B2	02/24/04	Yerxa et al.	514	47	12/19/01

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*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
<i>dm</i>	7.	International Preliminary Examination Report	10/01/2004	PCT	-	-		

OTHER REFERENCES		
(Including Author, Title, Date, Pertinent Pages, Etc.)		

done *10/15/05*

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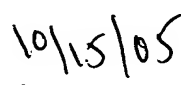
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<i>m</i>	1.*	6,040,297	03/21/00	De Flora	514	047	01/14/97	
	2.*	6,258,374	07/21/01	Freiss et al.	424	436	09/03/98	
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<i>m</i>	7.*	US2002/0156269 A1	10/24/02	Maeda et al.	536	26.21	04/12/02	
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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
<i>m</i>	8.*	EP 1 043 329 B1	08/28/02	EP	C07H	19/10	X	
	9.*	EP 1 191 032 A1	03/27/02	EP	C07H	19/10	X	
	10.*	WO 98/34942	08/13/98	WO	6	—		
	11.*	WO 00/30629	06/02/00	WO	—	—		
<i>m</i>	12.*	WO 01/87913	11/22/01	WO	—	—		
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<i>m</i>	13.*	Blaug, et al., "P2Y2 receptor agonists induce prolonged calcium, membrane voltage, conductance and fluid absorption increases in bovine RPE," <i>IOVS</i> , 41(4):S136 (2000) XP001088187						
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	17.	Maminishkis, et al., "The P2Y2 Receptor Agonist INS37217 Stimulates RPE Fluid Transport In Vitro and Retinal Reattachment in Rat," <i>IOVS</i> , 43(11): 3555-3566 (2002).						
<i>m</i>	18.	Meyer, et al., "Effect of INS37217, a P2Y2 Receptor Agonist, on Experimental Retinal Detachment and Electroretinogram in Adult Rabbits," <i>IOVS</i> , 43(11): 3567-3574 (2002).						

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u	19.	Nour, et al., "P2Y ₂ Receptor Agonist INS37217 Enhances Functional Recovery After Detachment Caused by Subretinal Injection in Normal and rds Mice," IOVS, 44(10): 4505-4514 (2003).
	20.*	Peterson, et al., "Extracellular ATP activates calcium signaling, ion, and fluid transport in retinal pigment epithelium," <i>Journal of Neuroscience</i> , 17(7):2324-2337 (1997) XP001087693
	21.*	Sillero, et al., (2',3'-Dideoxynucleoside triphosphates (ddNTP) and di-2',3'-dideoxynucleoside tetraphosphates (ddNp4ddN) behave differently to the corresponding NTP and NP4N counterparts as substrates of firefly luciferase, and dinucleoside tetraphosphatase and phosphodiesterases," <i>Biochemica et Biophysica Acta</i> 1334(2-3):191-199 (1997) XP002208651
	22.	Takahasi, et al., "Effect of Nucleotide P2Y ₂ Receptor Agonists on Outward Active Transport of Fluorescein Across Normal Blood-retina Barrier in Rabbit," <i>Experimental Eye Research</i> 78:103-108, (2004).
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u	24.*	Williams, M., "P ₂ Receptors as drug discovery targets," <i>Am. Chem. Soc.</i> 220 th , Medi-185 (2000) XP001085299
	25.*	Zhavrid, et al., "Dicytidine-5'-pyrophosphates with antiviral activity," XP002208653

Not considered
date not provided

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Spears

DIG-specific signal was detected using a chromophore reaction against the alkaline phosphatase, yielding purple/black staining. The tissues were also counterstained with nuclear fast red. The control sense probe (right) shows no specific labeling. Labeling with the anti-sense probe showed P2Y₂ receptor mRNA localization in scattered nuclei in the ganglion cell and inner nuclear layers and through the inner segment layer of photoreceptors. Strong labeling throughout the RPE was also detected, and in endothelial cells of the choroidal blood vessels.

Example 2. Effects of Synthetic P2Y₂ Agonist UP₄dC on Cloned Human P2Y₂ Receptors

The dinucleotide, [P¹-(uridine 5')-P⁴-(2'-deoxycytidine 5')-tetrphosphate tetrasodium salt](UP₄dC) INS37217, was tested for its activity (potency, efficacy, and selectivity) at cloned human P2Y receptor subtypes, which were stably expressed in 1321N1 astrocytoma cells. Activity was assessed using two *in vitro* indices of cell activation: 1) mobilization of intracellular calcium stores, and 2) accumulation of [³H]-inositol phosphates ([³H]-IP). UP₄dC was evaluated for activity in both assays against cells expressing the P2Y₁, P2Y₂, P2Y₄, or P2Y₆ receptors.

UTP and UP₄dC induced mobilization of cytosolic calcium in 1321N1 astrocytoma cells expressing human P2Y₂ (Figure 2) receptors with EC₅₀ values of 0.22 μM and 0.8 μM, respectively. The calcium response to 100 μM UP₄dC was 100% of the maximal response to UTP at P2Y₂ receptors. In conclusion, UP₄dC is a full agonist for calcium mobilization at P2Y₂ receptors compared to UTP.

UTP and UP₄dC stimulated [³H]-IP accumulation in 1321N1 cells expressing human P2Y₂ (Figure 3) receptors with an EC₅₀ values of 1.1 and 2.2 μM, respectively. The inositol phosphate response to 100 μM UP₄dC was approximately that of the maximal response to UTP. In conclusion, UP₄dC is a full agonist for inositol phosphate release at P2Y₂ receptors compared to UTP in the test system.

Example 3. UP₄dC Stimulates Fluid Absorption in Freshly Isolated RPE Monolayers

Fluid transport across freshly isolated, intact bovine and human fetal RPE monolayers was studied using a modified capacitance probe technique (Frambach, *et al.*, *Biophys. J.* 47(4):547-52 (1985); Hughes, *et al.*, *J Gen. Physiol.* 83(6):875-99 (1984)).

The RPE was mounted vertically in a modified Ussing chamber such that apical and